ON THE CAUSE OF THE RISE OF BLOOD-PRESSURE PRODUCED BY DIGITALIS.

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Speaking generally two views are held with regard to the method in which the marked rise of arterial tension, which follows the administration of digitalis, comes about. Some pharmacologists regard this as due entirely to the alteration in the activity of the heart, others hold that there occurs coincidently with this alteration in cardiac activity, a contraction of the arterioles, and that this latter phenomenon plays an important *rôle* in the rise of arterial tension.

The first of these views has received most of its support from German pharmacologists, and especially from Prof. Schmiedeberg, who speaking of the action of digitalis in the last edition of his *Arzneimittellehre*[1] states that if it exerts any contracting influence on the arterioles at all, this can only be of a transient nature. As we wish to examine this subject thoroughly before giving our own method of attacking the problem and its results, we think it will be profitable to summarily review the researches bearing upon this question.

Blake[2], working at the suggestion of Sharpey with the hæmodynamometer, found that the injection of an infusion made from ʒī, *i.e.* four grammes of the leaves, into the jugular vein of a dog caused the pressure in the femoral artery to rise from 5—8 inches. The introduction of larger quantities, into the carotid artery in a direction away from the heart produced a rise of blood-pressure of from 9—7 inches and this before the heart's action was affected. This latter was however in all probability not a pure result. Blake further noticed that after digitalis had been given the arterial pressure fell very slowly after the cessation of the cardiac beats, it in one case remaining $2\frac{1}{2}$ inches above the abscissa one minute after the stoppage of the heart. Traube[3], in his later works[4], was fully aware that digitalis

[1] Leipzig, 1895, p. 170.

[2] *Edinburgh Med. Journal*, li. 330. 1839.

[3] *Gesammelte Beiträge*, Band i. 259.

[4] *Berlin. klin. Woch.* ii. 369. 1870.

produced an effect on the vessels, and observed that in cases where digitalis had been given in large doses, despite frequent and irregular cardiac action the arterial tension kept high, a considerable fall of pressure only taking place immediately before death. Lenz[1] showed clearly that there was another factor than increased cardiac activity in the production of the rise of arterial tension which follows the injection of digitalis. According to this observer (Exp. XIV.) coincidently with the rise of blood-pressure, the pulse remaining constant, a marked diminution in the velocity of the blood stream took place, as follows:

	Pulse Rate	Blood-pressure	Velocity
Normal	122	102	114
Digitalis	123	130	25

This result can only be explained on the assumption that contraction of the vessels had taken place. Von Bezold[2] compared the rate of fall of arterial tension after division of the spinal cord, under normal conditions and under digitalis. He found that under digitalis the rate of fall was little more than half that occurring under normal conditions. This diminution in the rate of fall of arterial tension is to be explained by contraction of the arterioles having occurred under digitalis, and thus an increased resistance having been offered to the emptying of the arterial system. With regard to Boehm's[3] paper we do not think that his conclusions are justified by his results. His observations on the effect of digitalis after division of the spinal cord we have not been able to confirm.

In 1868 some experiments were made by one of us (Brunton) in conjunction with A. B. Meyer[4]. These experiments showed that the descent of blood-pressure during the cardiac diastole became more gradual after the administration of digitalis than before. Since the blood in the aortic system is entirely cut off from the heart during the cardiac diastole by the closed aortic valves, the rate at which the blood-pressure falls during each diastole depends solely upon the conditions obtaining in the aorta and its branches and has nothing whatever to do with the heart. Hence the detailed examination of this part of the

[1] Exp. de ratione inter pulsus frequentiam sang. pressionem lateratem et sang. fluentis celeritatem obtinenti, *Dorpat.* 1853.

[2] *Ueber die Innervation des Herzens. Abtheilung*, II. p. 205. 1863.

[3] *Pflüger's Archiv*, v. p. 153. 1872.

[4] *Journ. of Anat. and Phys.*, VII. p. 134.

pulse wave furnishes us with a means of studying the action of digitalis upon the vessels quite apart from its action on the heart.

The factors which determine the rapidity of descent of the blood-pressure and consequently of the kymographic curve during diastole are, (1) the initial pressure in the aorta at the beginning of diastole, (2) the relative patency of the arterioles through which the blood escapes from the arteries into the veins. If the initial pressure be constant the fall of blood-pressure will be more or less rapid, and the descent of the kymographic curve more or less abrupt, according to the patency of the arterioles. If they are dilated the blood will flow quickly through them, the blood-pressure will fall rapidly, and the descent of the kymographic curve will be sharp, but if the arterioles be contracted the flow of blood through them will be slow, the fall of blood-pressure will be gradual and the descending limb of the kymographic curve will be obtuse. If on the other hand the arterioles remain constant and the initial pressure varies, it will be found that a high initial pressure will cause a more rapid flow and thus produce changes in the kymographic curve resembling those produced by dilated arteries under constant initial pressure, whilst diminished initial pressure with constant arterioles will have upon the kymographic curve a similar effect to contracted arterioles with constant initial pressure. Under the influence of digitalis the initial pressure is raised, and yet the blood-pressure during the cardiac diastole, instead of falling more quickly as it ought to do, if the arterioles remained unchanged, falls more slowly, and the descending limb of the kymographic becomes more obtuse. This difference in the rate of fall of the descending limb of the pulse curve under digitalis, is seen in the curve which is reproduced below (Fig. 1). In this curve I shows the normal pulse, II the beginning

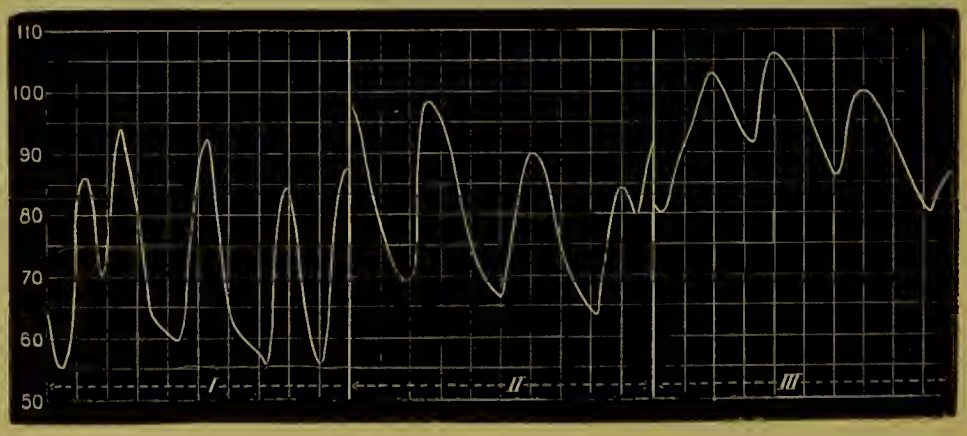


Fig. 1.

of the action of digitalis, the pressure being slightly raised, and the diastolic descent less sudden. III, the more pronounced action of digitalis, the pressure being further increased, the pulse slowed, and the diastolic descent still more gradual.

Görzt[1] raises the objection that such a diminution in the acuteness of the descent of pressure during diastole would occur under any condition which causes a rise of blood-pressure, such as that which succeeds stimulation of the vagus: such is not the case. The argument does not rest at all upon the depth to which the diastolic limb of the pulse wave descends, but upon the rapidity of its descent; the apex of the normal pulse forming an acute angle, while that of the digitalis pulse forms a less acute one. Further upon examining the above curve it will be seen that this peculiar form of the pulse under the influence of digitalis does not occur only during a rise of pressure but remains the same during a respiratory fall of blood-pressure.

Williams[2] showed that in the frog a rise of blood-pressure equal to that caused by digitalis could be produced by applying the drug to the frog's heart connected with a system of glass tubes to represent the arteries. He thus proved that the increased action of the heart in the frog under digitalis was sufficient in amount to explain the rise of blood-pressure following the administration of this drug, without any coincident contraction of the arterioles. This we do not doubt, but his further remarks on the action of the drug in mammals require consideration. To the theory that the arterioles in mammals are contracted by digitalis Williams objects that if narrowing of the vessels took place to any considerable extent the pulse volume in the carotid could not undergo an increase. The contraction produced by digitalis is, by all those who hold that it takes place, located in the arterioles, where the unstriped muscular tissue is, relatively to the mass of the arterial wall, much greater than in the large arteries. Contraction of the arterioles would not *per se* appreciably affect the occurrence of an increase in amplitude of the carotid pulse. In migraine increased pulsation in the carotid has been observed coincidently with contraction of its peripheral branches. Williams further states that the changes following digitalis are the same in the circulatory system of his frog's heart apparatus, the tubes representing the arteries of which are incapable of contraction, as in the dog. As a proof of this statement he draws attention to the two curves which are reproduced below (Fig. 2), the one (upper) representing the

[1] *Dissert. Dorpat*, 1873.

[2] *Arch. für exp. Path. u. Pharm.*, XIII. p. 1. 1881.

effects of digitalis upon the circulatory system of the dog, the other (lower) those of helleborin on an artificial circulatory apparatus consisting of the frog's heart and a system of rigid tubes. We cannot regard the changes in these two cases as identical. In the case of the frog's circulatory apparatus the increase in blood-pressure is coincident with the

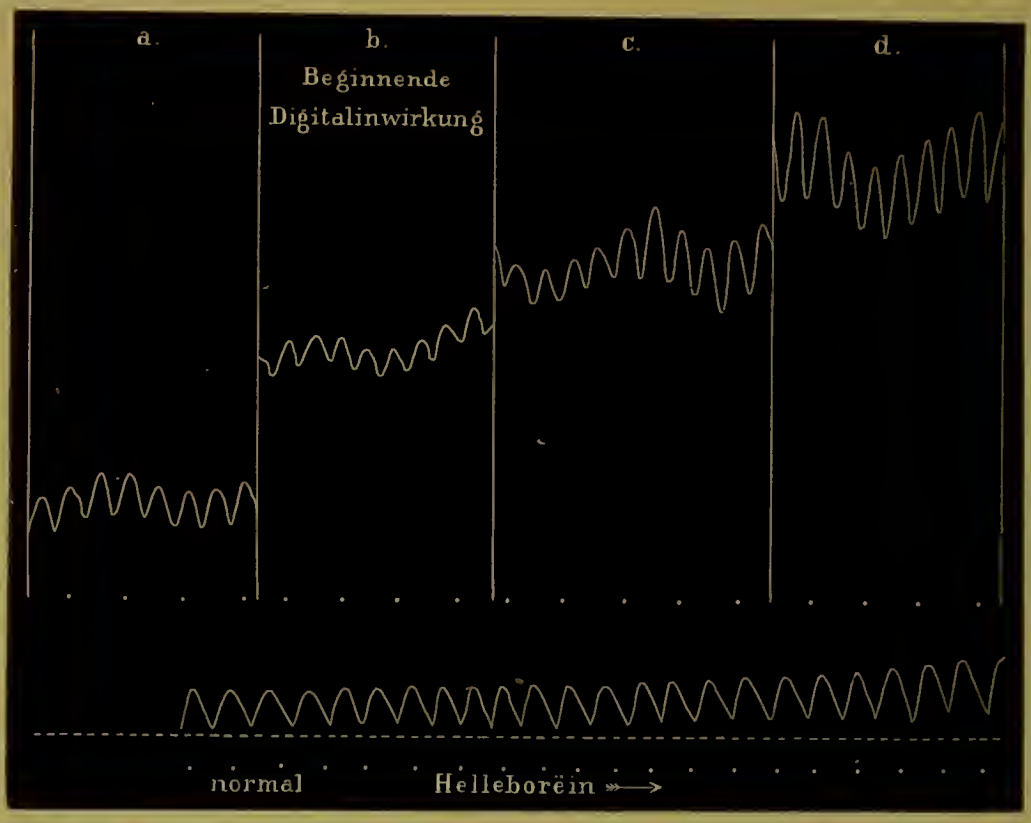


Fig. 2.

increase in cardiac activity, *i.e.* with the amount of fluid expelled by the heart in a given time interval. In the dog this is not the case.

In division *b* of the upper of the two tracings which is marked "beginnende Digitalinwirkung" the cardiac activity is not increased, but a considerable rise of blood-pressure has taken place. It can also be shown (Fig. 3) that in the late stages of digitalis poisoning when the cardiac activity has become markedly reduced, a high arterial tension is still maintained. The tracing reproduced in Fig. 3 shows the effect of the introduction into the femoral vein of a cat of a gradually increasing dose of the infusion of digitalis leaves (B.P). The blood-pressure was taken from the left carotid artery. At x^1 a small dose, one drachm (4 c.c.), of the infusion was injected into the femoral vein. The recording cylinder was stopped until the action of the drug had made itself mani-

fest. The diminished frequency and increased volume of the cardiac pulsations are shown between x^1 and x^2. At x^2 the recording cylinder

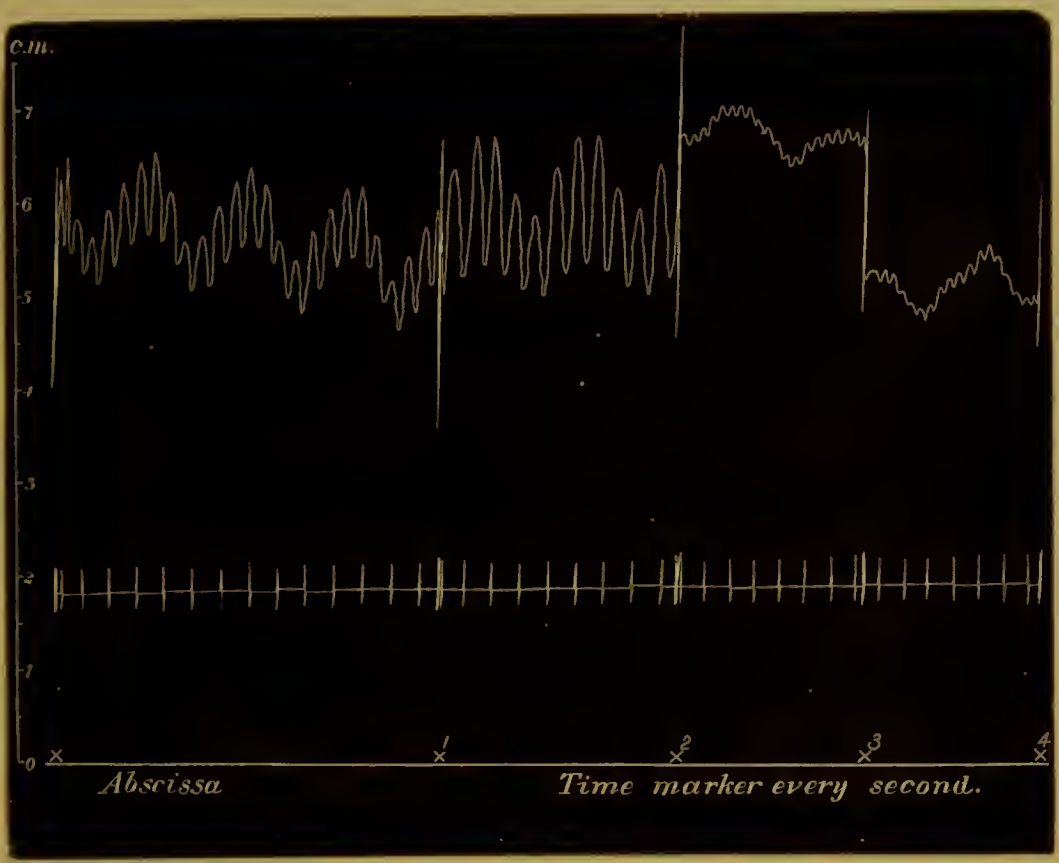


FIG. 3.

was again stopped and two fluid drachms more of the infusion were injected into the femoral vein. The heart, as is shown on the tracing between x^2 and x^3, became feeble and rapid, but the blood-pressure rose. At x^3, after stopping the recording cylinder, a further dose of digitalis was injected, with the result that the heart became irregular and the blood-pressure considerably lowered. We regard the maintenance of the increased pressure, between x^2 and x^3 as due almost entirely to the contracted state of the arterioles, and the lowering of pressure which occurs after x^3 as due to a condition of paralysis of the arterioles supervening upon an increased dose of the drug. The change in cardiac activity between x^2 and x^3 and x^3 and x^4, is not in itself sufficient to explain the fall of blood-pressure occurring at x^3, after the further dose of digitalis. From the experiments on the general blood-pressure we pass to those (i) in which the arteries were directly observed and (ii) perfusion experiments.

Galan[1] observed contraction in the vessels of the frog's web under digitalis. Legroux[2] observed contraction of the vessels and lowering of the temperature of the rabbit's ear under digitalis. Milner Fothergill[3] observed contraction of the vessels of the frog's web. Ackerman[4] observed contraction of the mesenteric vessels of the rabbit after the administration of digitalis with the spinal cord intact and divided. Koppe[5], Klug[6] and others have observed contraction of the vessels of the rabbit's ear.

Donaldson and Stevens[7] perfused the general circulatory system of curarized terrapins with a ·0005 % solution of digitaline in normal saline solution, and succeeded by this means in reducing the rate of outflow to half its normal value. Upon reperfusing with normal saline solution the rate of outflow returned to the normal. Ringer and Sainsbury[8] using a ·005 % solution of digitaline (Morson) for perfusion reduced the outflow from the venous canula from 98 c.c. to 12 c.c. per 5 min. Upon cessation of the digitalis however the outflow did not return to the normal. Schäfer[9] performed similar experiments on mammals with double the strength of digitaline and obtained the same result. Kobert[10] perfused digitaline dissolved in defibrinated blood from the same animal in the strength of from ·0002 to ·0006 p.c. through excised organs (kidneys and liver), this reduced the outflow per unit of time from 17 to 69 %. These results remained constant in decomposing organs and at low temperatures (below 15° C.) from which the author inferred that the drug acted upon the muscular rather than upon the nervous elements in the vascular wall. The objections that Prof. Schmiedeberg makes to these perfusion experiments are[11], (i) That the proportion of poison in the perfused blood in these experiments greatly exceeded the amount requisite to produce a considerable rise of blood-pressure when introduced into the circulation of living animals. (ii) The phenomenon, *i.e.* contraction of the vessels was not constant, the opposite often occurring, especially in the kidney. (iii) That the contraction of the vessels occurred in excised organs which had begun to decompose. In this connection we would point out firstly that the

[1] *Consid. physiologiques sur l'action de digitale.* Thèse, Paris, 1861.

[2] *Gazette hebd.*, 1867, pp. 113 et seq. [3] *Brit. Med. Journ.*, 1871, II. p. 27.

[4] *Naturforscher Versammlung*, Rostock, 1871; also *Rich. Volkmann's klin. Vortr äge Journ. Medicin*, vol. I. 389. [5] *Inaug. Dissert. Dorpat*, 1874.

[6] *Archiv für Anat. u. Phys.*, Supplement, 1880, p. 470.

[7] This *Journal*, IV. p. 165. 1883.

[8] *Med. and Chi. Soc. Trans.*, 1884, vol. LXVII. [9] *Ibid.* p. 84.

[10] *Archiv für exp. Path. u. Pharm.*, XXII. p. 77. 1887.

[11] *Arzneimittellehre*, 1895, p. 170.

proportion of digitaline used in the perfusion experiments does not exceed the amount which alone gives results with the excised frog's heart, and is less than that used for this purpose by Boehm[1] and Williams[2]. In the experiments of Donaldson and Stevens there can be no question of an excess of dose, since the effect was quickly made to disappear by perfusing saline solution and again to reappear upon circulating the digitalin solution. The proportion used by Ringer and Sainsbury was larger and their effects more persistent. Prof. Schmiedeberg's second objection which refers only to Kobert's experiments is that these effects occurred in organs undergoing decomposition. We do not see that this fact is any evidence against digitalis acting on the muscular structure in the walls of the arterioles, and this was the view taken by Kobert[3].

With regard to the question whether digitalis contracts the vessels of the kidney, we would first of all point out that this is entirely a different question from the one we are considering; even supposing that strong evidence existed that digitalis exerted no contracting influence on the renal vessels this would by no means justify the generalization that it exerted no such influence on the other vessels. The original of Kobert and Thompsen's[4] monograph which Schmiedeberg quotes as showing that digitalis dilates renal vessels has unfortunately not been accessible to us, nor has Goldenburg's[5], in which the author states that digitalis contracts all the vessels of the body except those of the kidney. The oncographic results of Bradford[6] are however entirely in accordance with those of Kobert on the excised kidney. Bradford found that a marked diminution in the volume of the kidney occurred under digitalis, and that this was remarkably persistent, lasting half-an-hour, Kobert found that the constricting influence of the digitalined perfusion solution lasted in one case 38 min. From the above abstract of the observations of previous workers we are justified in saying that there is very strong evidence that digitalis exerts a contracting action on the arterioles.

The method we have adopted to examine the action of digitalis on

[1] *Loc. cit.*, p. 171. Boehm added from 1—6 drops of a 10 % solution of digitalin (Merk) to the supply reservoir of a Ludwig and Coats' frog's heart transfusion apparatus. He speaks of from 2—5 drops of a 5 % solution injected under the skin as "mittlere Dosen" for frogs (p. 160).

[2] *Loc. cit.* Williams added "a few drops" of a 1 % solution of digitalin to the reservoir of his frog's heart apparatus.

[3] *Loc. cit.* [4] *Dissert. Dorpat*, 1886. [5] *Dissert. Dorpat*, 1893.

[6] This *Journal*, 1887, VIII. p. 128.

the vessels consists essentially in (i) inhibiting the heart for the same length of time under normal conditions and after the injection of digitalis, and (ii) comparing the rate and extent of the ensuing fall of blood-pressure in the carotid, in the two cases. It is obvious that if the heart is arrested in each case for the same time both the extent and the rate of the fall of the blood-pressure in the carotid will depend upon the initial pressure at the time of cardiac inhibition, and the relative contraction or dilatation of the peripheral vessels, through which the great arteries empty themselves into the veins. Any factor tending to increase the initial pressure or dilate the peripheral vessels will increase the amount of the fall in a given time, and *vice versâ*. The two following curves are blood-pressure tracings from the left carotid of a medium-sized rabbit, Fig. 5 being taken consecutively to Fig. 4. In Fig. 4, at the point marked *O* on the bottom (electric signal) line of the figure, the left vagus was stimulated by an induction current, immediately afterwards the heart became inhibited and remained so for $3\frac{3}{4}$ seconds; during this time the blood-pressure in the carotid fell from 50 mm. to 13 mm. or 37 mm.

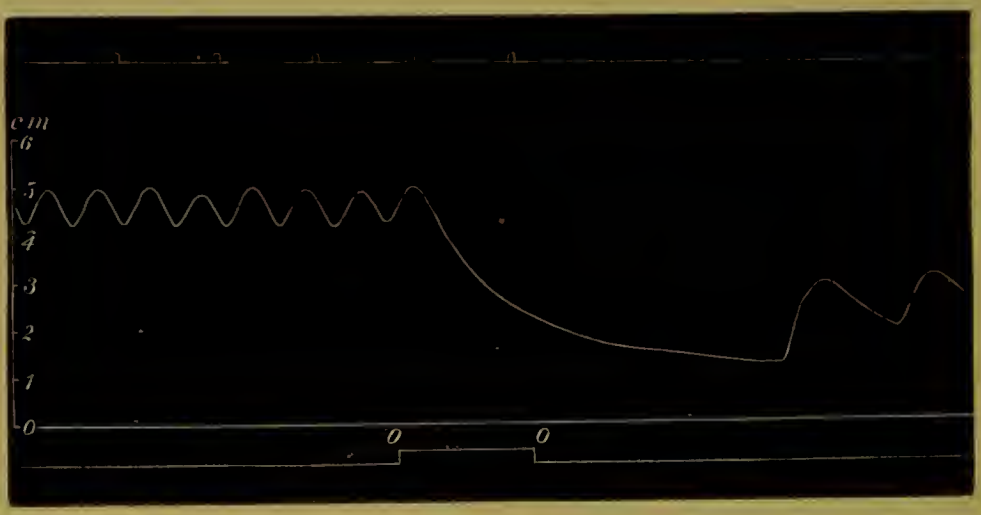


Fig. 4.

Fig. 5 shows the effect of a small dose, ·02 grm, of digitalin[1] upon the fall of pressure consequent upon vagus stimulation. Upon comparing this curve with the last, Fig. 4, it will be seen that the effect of this dose of digitalin, which was injected into the femoral vein, was to slow and increase the volume of the pulse, and to raise the pressure 10 mm. At *O'* of the electric signal line the left vagus was again stimulated with the same strength of induction current, but, as will be seen, for a longer time. As a result of this stimulation the heart became

[1] The digitalin used was that contained in Messrs Burroughs and Welcome's tabloids.

inhibited for four seconds. At the time of cardiac inhibition the pressure in the carotid amounted to 58 mm., at the end of $3\frac{3}{4}$ seconds

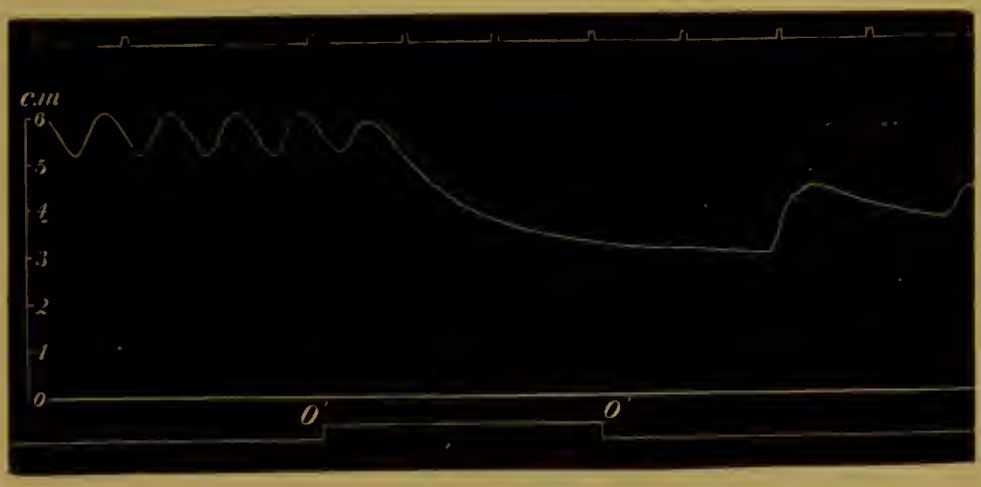
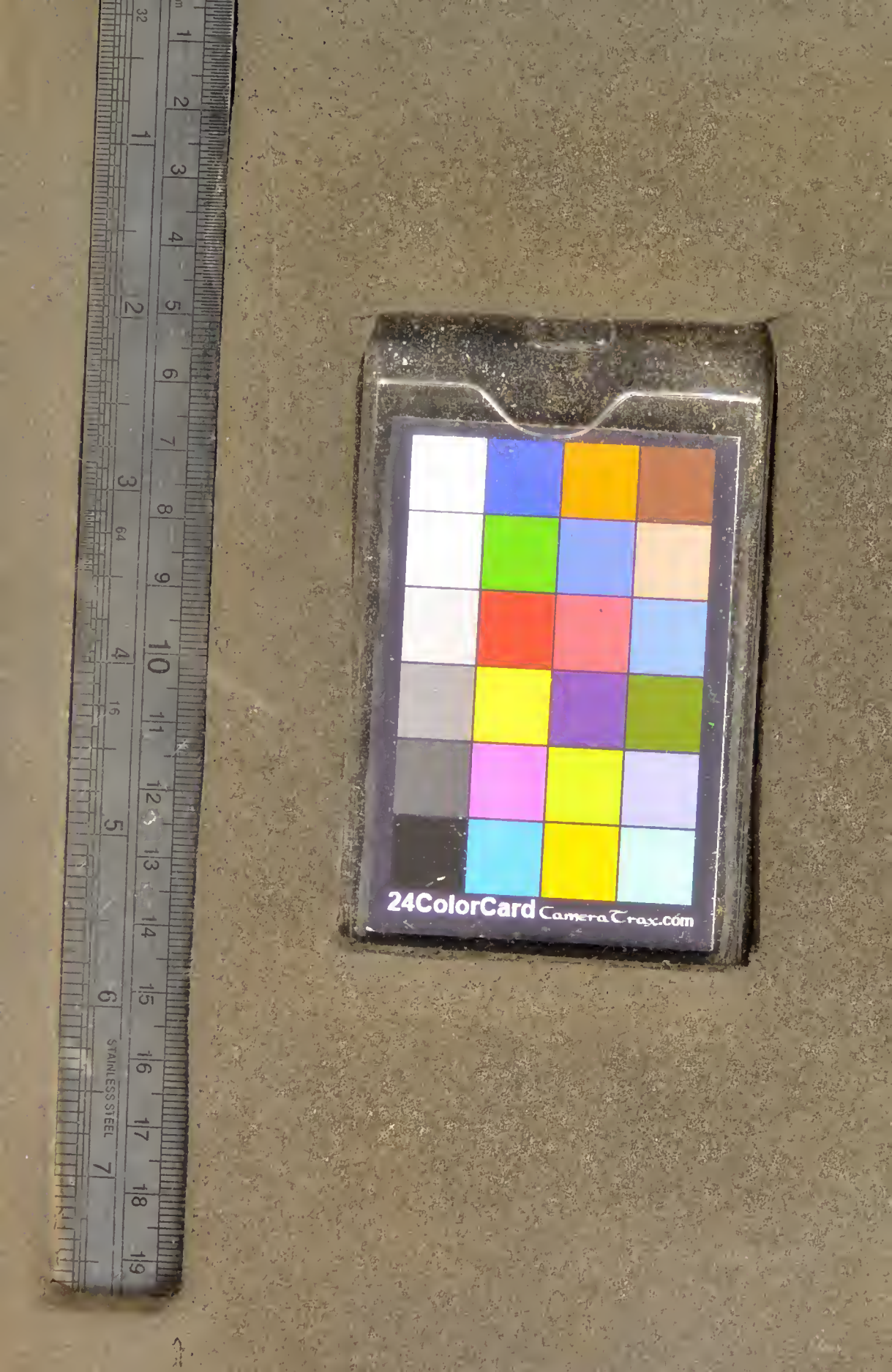


Fig. 5.

of cardiac still-stand it stood at 32 mm. In other words, with an initial pressure 10 mm. higher than in the last experiment, the fall of pressure during a cardiac still-stand of an equal length of time amounted to 10 mm. less. This diminished rate of fall under increased pressure can, we think, only be explained by assuming that the dose of digitalin given, in addition to slowing and increasing the volume of the pulse, contracted the peripheral vessels.

The experiments described above confirm von Bezold's[1] observations that after the administration of digitalis the arterial pressure upon division of the cord falls less rapidly than under normal conditions. They further confirm the results of Lenz[1]. They also, taken with the perfusion experiments, explain how with a rapid and irregular heart, a heart propelling less blood, but doing more work, on account of the raised pressure, than a normal heart, the high arterial tension is maintained. That the heart under the influence of digitalis is *per se* capable of producing a rise of blood-pressure was shown clearly by Williams[1]. We are not in this paper attempting to disprove this. Our contention simply is that digitalis, concomitantly with its cardiac tonic, exerts a vascular tonic action. Further that this vascular tonic action is not unimportant and transient but by increasing the resistance to the cardiac systole must be taken seriously into consideration in estimating the therapeutic advantages to be obtained from this drug, as well as the risks which may arise from its use in unsuitable conditions.

[1] *Loc. cit.*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